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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904500 for a patent by GRIFFITH UNIVERSITY as filed on 21 August 2003.

WITNESS my hand this
Thirty-first day of August 2004

LEANNE MYNOTT
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AUSTRALIA

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PROVISIONAL SPECIFICATION

Applicant:

GRIFFITH UNIVERSITY

Invention Title:

NOVEL COMPOUNDS II

The invention is described in the following statement:

NOVEL COMPOUNDS II

Technical Field

The present invention relates to novel sulfenamides and their derivatives that have physiological activity, particularly an antimicrobial action, methods for their synthesis, pharmaceutical compositions containing them and method of treatment of patients, in particular, those suffering a microbial infection.

Background Art

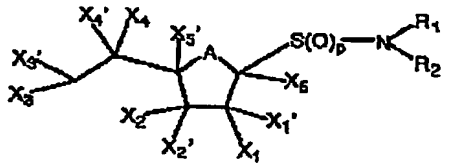
Many bacterial diseases once thought to be on the decline are beginning to re-emerge and annually devastate populations in many countries. This problem is amplified by the emergence of many new drug resistant strains of the microorganisms that cause these diseases. Our interest in the development of carbohydrate-based antimicrobial agents (see, for example, von Itzstein, Wu, et al., 1993; Kok, Campbell, Mackey, & von Itzstein, 1996; Fazli, Bradley et al., 2001) and in glycofuranose chemistry (Owen & von Itzstein, 2000) has led to the discovery of a new class of antimicrobial agents described below. Although significant chemistry and biology has been published (see, for example, Marino, Marino, Miletti, Alves, Colli, & de Lederkremer, 1998; Miletti, Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang & Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe, Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de Lederkremer, Cirelli & Sznaidman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer, Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; Ernst, Hart & Sinay, 2000) in the area of glycofuranose chemistry and biology NONE to date provides compounds that have significant antimicrobial activity. Carbohydrate mimics based on isosteres of the ring structure are well known in the literature and often present interesting biological activities (see, for example, Chapleur, 1998; Lillelund,

Jensen, Liang, & Bols, 2002; Kok, Campbell, Mackey, & von Itzstein, 1996).

Disclosure of the Invention

The present invention is concerned generally with novel sulfenamides and their derivatives that have physiologic activity, in particular, an antimicrobial action.

In a first aspect of the present invention there is provided a compound of general formula (I):



wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted aryl, optionally substituted acyl and a carbohydrate moiety;

or R_1 and R_2 together with the nitrogen atom from which they depend form a saturated or unsaturated, optionally substituted heterocyclic group which may include additional heteroatoms selected from the group consisting of O, N and S, or R_1 and R_2 together with the nitrogen atom from which they depend form an optionally substituted lactam or cyclic imide moiety;

A is selected from the group consisting of O, S, SO, SO_2, Se, Te, NR_8, $CR_9R'_9$ and C(O);

X_1 is selected from the group consisting of OR_3, SR_3, $NR_3R'_3$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_3$, $-N(C=(Z)(T)_nR_3)_2$, N_3, CN, OCN, SCN, OSO_3R_3, OSO_2R_3, $OPO_3R_3R'_3$, $OPO_2R_3R'_3$, $S(O)R_3$, $S(O)_2R_3$, $S(O)_2OR_3$, $PO_3R_3R'_3$, $NR_3NR'_3R''_3$, $SNR_3R'_3$, $NR_3SR'_3$, SSR_3 and R_3, or is an oxo group, =S, $=NOR_3$ or $=CR_3R'_3$ and X_1' is absent, or X_1 is C=(Z) and R_2 is bond thereto so as to form a cyclic moiety $-C=(Z)NR_1S(O)_p-$;

X_2 is selected from the group consisting of OR_4, SR_4, $NR_4R'_4$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_4$, $-N(C=(Z)(T)_nR_4)_2$, N_3, CN, OCN, SCN, OSO_3R_4, OSO_2R_4, $OPO_3R_4R'_4$, $OPO_2R_4R'_4$, $S(O)R_4$, $S(O)_2R_4$, $S(O)_2OR_4$, $PO_3R_4R'_4$, $NR_4NR'_4R''_4$, $SNR_4R'_4$, $NR_4SR'_4$, SSR_4 and R_4, or is an oxo group, =S, $=NOR_4$ or $=CR_4R_4$ and X_2' is absent;

X_3 is selected from the group consisting of OR_5, SR_5, $NR_5R'_5$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_5$, $-N(C=(Z)(T)_nR_5)_2$, N_3, CN, OCN, SCN, OSO_3R_5, OSO_2R_5, $OPO_3R_5R'_5$, $OPO_2R_5R'_5$, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2OR_5$, $PO_3R_5R'_5$, $NR_5NR'_5R''_5$, $SNR_5R'_5$, $NR_5SR'_5$, SSR_5 and R_5, or is an oxo group, =S, $=NOR_5$ or $=CR_5R'_5$ and X_3' is absent;

X_4 is selected from the group consisting of OR_6, SR_6, $NR_6R'_6$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_6$, $-N(C=(Z)(T)_nR_6)_2$, N_3, CN, OCN, SCN, OSO_3R_6, OSO_2R_6, $OPO_3R_6R'_6$, $OPO_2R_6R'_6$, $S(O)R_6$, $S(O)_2R_6$, $S(O)_2OR_6$, $PO_3R_6R'_6$, $NR_6NR'_6R''_6$, $SNR_6R'_6$, $NR_6SR'_6$, SSR_6 and R_6, or is an oxo group, =S, $=NOR_6$ or $=CR_6R'_6$ and X_4' is absent;

or one of X_1 and X_2, X_2 and X_5', X_5' and A when A contains a carbon or nitrogen atom, X_5 and A when A contains a carbon or nitrogen atom, and X_5 and X_1 together constitute a double bond, or X_5' and X_4 or X_3 and X_4 together constitute a double bond, or X_1 and X_2, X_2 and X_3, X_2 and X_4, X_3 and X_4, X_1 and X_1', X_2 and X_2', X_3 and X_3' or X_4 and X_4' together form a ring;

m and n are independently zero or one and Y, Z and T are independently selected from the group consisting of O, S, and NR_{10}

D is zero, one or two;

X_5 is selected from the group consisting of hydrogen, CN, $-C=(Z)(T)_nR_{11}$, $S(O)R_{11}$, $S(O)_2R_{11}$, $S(O)_2OR_{11}$, $PO_3R_{11}R'_{11}$, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

X_1', X_2', X_3', X_4', and X_5' are the same or different and are selected from the group consisting of hydrogen, CN, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

R_3, R'_3, R''_3, R_4, R'_4, R''_4, R_5, R'_5, R''_5, R_6, R'_6, R''_6, R_7, R_8, R_9, R'_9, R_{10} and R_{11} are the same or different and are selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted acyl and a carbohydrate moiety;

with the proviso that where A is oxygen p is one or two, and that at least two of X_1, X_2, X_3 and X_4 are other than hydrogen or a group linked to the ring through a carbon-carbon bond;

or a pharmaceutically acceptable salt thereof.

It will be appreciated that the manner of representing substituents in the foregoing general formula does not imply any particular stereochemistry or orientation for the substituents.

The term "alkyl" used either alone or in a compound word such as "optionally substituted alkyl" or "optionally substituted cycloalkyl" denotes straight chain, branched or mono- or poly- cyclic alkyl. Examples of straight chain and branched C alkyl include methyl. ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-

dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl and the like.

The term "alkenyl" used either alone or in compound words such as "alkenyloxy" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as defined above. Examples of C_{4-30} alkenyl include butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "acyl" used either alone or in compound words such as "optionally substituted acyl" or "optionally substituted acyloxy" denotes an aliphatic acyl group or an acyl group containing an aromatic ring, which is referred to as aromatic acyl, or a heterocyclic ring, which is referred to as heterocyclic acyl, preferably C_{1-30} acyl. Examples of acyl include straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacrylyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; and heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl.

The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "optionally substituted aryloxy" or "optionally substituted heteroaryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphtyl, tetrahydronaphthyl, anthracenyl,

dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, pyrrolyl, furanyl, imadazolyl, pyrrolydinyl, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, a carbocyclic aromatic ring system contains 6-10 carbon atoms and an aromatic heterocyclic ring system contains 1 to 4 heteratoms independently selected from N, O and S and up to 9 carbon atoms in the ring.

The term "heterocyclyl" or equivalent terms such as "heterocyclic" used either alone or in compound words such as "optionally substituted saturated or unsaturated heterocyclyl" denotes monocyclic or polycyclic heterocyclyl groups containing at least one heteroatom atom selected from nitrogen, sulphur and oxygen. Suitable heterocyclyl groups include N-containing heterocyclic groups, such as, unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidino or piparazinyl;

unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, such as, thienyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

The term "carbohydrate" denotes a carbohydrate residue or a functionalised or deoxygenated carbohydrate residue, and includes monosaccharides and oligosaccharides. A carbohydrate residue is an acyclic polyhydroxy-aldehyde or ketone, or one of their cyclic tautomers, and includes a compound resulting from reduction of the aldehyde or keto group such as alditols. Oxygen atoms may be replaced by hydrogen or bonds to a halogen, nitrogen, sulfur or carbon atoms, or carbon-oxygen bonds such as in ethers or esters may be introduced. Examples of carbohydrates include but are not limited to D-galactofuranose, *N*-acetyl-D-galactofuranose, D-glucofuranose, *N*-acetyl-D-glucofuranose, D-galactopyranose *N*-acetyl-D-galactopyranose, D-glucopyranose and *N*-acetyl-D-glucopyranose and their equivalents where oxygen atoms have been replaced in selected positions with hydrogen or bonds to halogen, nitrogen, sulfur or carbon, as well as oligosaccharides containing these moieties.

In this specification "optionally substituted" means that a group may or may not be further substituted

with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphanyl, carboalkoxy, carboaryloxy, mercapto, alkylthio, benzylthio, acylthio, phosphorus-containing groups and the like, provided that none of the substituents outlined above interferes with the formation of the subject compound.

Any of the moieties whose length is defined in terms of the number of carbon atoms present may possess any number of carbon atoms within the specified range. Nevertheless, within this range certain species will be preferred due to factors such as availability and cost of precursors and ease of synthesis, as well as efficacy. In particular, such moieties containing 4 to 24 carbon atoms, preferably 6 to 12 carbon atoms, more preferably 8 to 10 carbon atoms and most preferably 8 carbon atoms are preferred for reasons of cost and availability of precursors, ease of synthesis and efficacy.

In a particularly preferred embodiment of the present invention, A is oxygen and p is one or two, or A is S or NR_8, and one of R_1 or R_2 is C_{4-30} alkyl and the other is hydrogen or C_{4-30} alkyl or R_1 and R_2 together with nitrogen atom from which they depend form a saturated or unsaturated heterocyclic ring containing said nitrogen atom as the single heteroatom.

More preferably, one of R_1 or R_2 is C_{4-24}, preferably C_{6-12}, alkyl and other is hydrogen or C_{4-24}, preferably, C_{6-12}, alkyl. Advantageously, both R_1 and R_2 are C_{4-30} alkyl, preferably C_{8-24}, more preferably C_{6-12}

alkyl. The alkyl groups are the same or different but most conveniently the same.

X_1, X_2, X_3 and X_4 may be any combination of substituents, but it is preferred that at least two of these moieties be other than hydrogen or a group linked to the ring through a carbon-carbon bond. Preferably, at least two of X_1, X_2, X_3 and X_4 are moieties linked to the ring through a carbon-oxygen bond, for example, in the case of X_1, OR_3, OSO_3R_3 and $OPO_3R_3R'_3$.

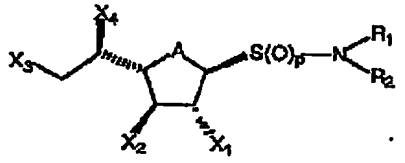
Preferably X_1 is OR_3. Advantageously R_3 is hydrogen or acyl, preferably C_{1-30} acyl.

Preferably X_2 is OR_4. Advantageously R_4 is hydrogen or acyl, preferably C_{1-30} acyl.

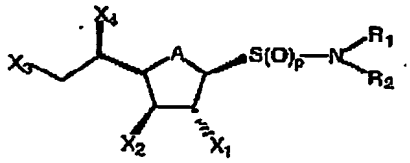
Preferably X_3 is OR_5. Advantageously R_5 is hydrogen or acyl, preferably C_{1-30} acyl.

Preferably X_4 is OR_6. Advantageously R_6 is hydrogen or acyl preferably C_{1-30} acyl.

Typically the compounds of the invention are galactofuranosyl compounds, and therefore have the configuration illustrated in general formula (Ia):



Alternatively, the compounds of the invention are glucofuranosyl derivatives having the general formula (Ib):



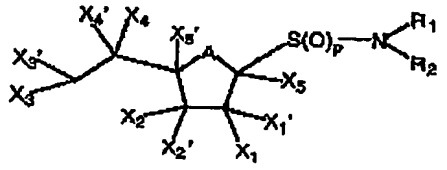
Advantageously the sulfenamide of general formula (I) is selected from the oxides of group consisting of

N,N-didecyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dihexyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-didecyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dihexyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-1-thio-β-D-glucofuranosyl)sulfenamide and *N,N*-dioctyl-*S*-(1-thio-β-D-glucofuranosyl)sulfenamide.

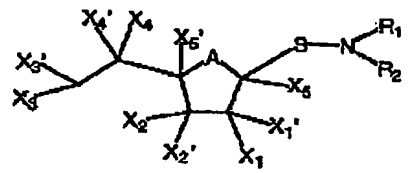
In a particularly preferred embodiment of the invention the sulfenamide of general formula (I) is an oxide of *N,N*-didecyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide or *N,N*-dihexyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, most particularly, *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide.

In another particularly preferred embodiment the sulfenamide of general formula (I) is a thio- (A = S) or aza- (A = NR_9) analogue of *N,N*-didecyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide or *N,N*-dihexyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide, most particularly of *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfenamide.

According to a second aspect of the present invention there is provided a method of preparation of a compound of general formula (I) where A is oxygen and p is one or two:



comprising reacting a compound of general formula (II):



Wherein R_1 and R_2, and X_1, X_1', X_2, X_2', X_3, X_3', X_4, X_4', X_5 and X_5', are as defined above with the proviso that none of R_2, R'_2, R''_2, R_3, R'_3, R''_3, R_4, R'_4, R''_4, R_5, R'_5, R''_5, R_6, R'_6 and R''_6 is hydrogen but, instead, is a protecting group;

with an oxidising agent;

and, optionally

removing the protecting groups.

Typically the oxidising agent is 3-chloroperbenzoic acid. A number of methods have been developed to oxidise sulfenamides as disclosed, for example, in Craine and Raban, 1989; Glass & Swedo, 1977; Haake, Gebbing, & Benack, 1979; the contents of which are incorporated herein by reference. Suitable protecting groups are well known to the person skilled in the art and in this case the benzoyl group is preferred. Benzoyl protecting groups are typically removed through hydrolysis with sodium methoxide in methanol. Methods for the preparation of compounds of general formula (II) are known in the art as disclosed, for example, in Craine and Raban, 1989; Owen & von Itzstein, 2000; the contents of which are incorporated herein by reference. An extensive array of methodologies has been developed to manipulate each position of the furanose template as disclosed, for example, in Marino, Marino, Miletti, Alves, Colli, & de Lederkremer, 1998; Miletti, Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang & Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe, Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de Lederkremer, Cirelli & Sznaidman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer; Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; Ernst, Hart & Sinay, 2000;

the contents of which are incorporated herein by reference.

According to a third aspect of the present invention there is provided a method for the treatment of a disease, particularly a microbial infection, comprising administering to a patient a therapeutically effective amount of a compound of general formula (I).

According to a fourth aspect of the present invention there is provided the use of a compound of general formula (I) in the manufacture of a medicament, particularly for use in the treatment of a microbial infection.

As used herein, the term "therapeutically effective amount" means an amount of a compound of the present invention effective to yield a desired therapeutic response, for example to prevent or treat a disease which by administration of a pharmaceutically-active agent.

The specific "therapeutically effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition and clinical history of the subject, the type of animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compound or its derivatives.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent, excipient or vehicle for delivering the compound of general formula (I) to the subject. The carrier may be liquid or solid, and is selected with the planned manner of administration in mind.

The compound of general formula (I) may be administered orally, topically, or parenterally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, intracranial, injection or infusion techniques.

The invention also provides suitable topical, oral, aerosol, and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compounds of the invention may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. The tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be, for example, inert diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as corn starch or alginic acid; binding agents, such as starch, gelatin or acacia; or lubricating agents, such as magnesium stearate, stearic acid or talc. The tablets may be uncoated, or may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U. S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

The compound of general formula (I) of the invention can be administered, for *in vivo* application, parenterally by injection or by gradual perfusion over time independently or together. Administration may be intravenously, intra-arterial, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For *in vitro* studies the agents may be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as, for example, anti-microbials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

The compounds of general formula (I) are antimicrobial agents which are active, in particular but not limited to, against *Mycobacterium* including *Mycobacterium tuberculosis*, *M. avium intracellulare*, *M. fortuitum*, *M. abscessus* and rapid growing atypical Mycobacterial strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus* and *S. aureus* (Coagulas-negative) and *Enterococci* species. The compounds of general formula (I) are particularly useful in treating infections involving these organisms.

Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing infection, and/or may be therapeutic in terms of a partial or complete cure of an infection. "Treating" as used herein covers any treatment of, or prevention of infection in a vertebrate, a mammal, particularly a human, and includes: preventing the infection from occurring in a subject that may have been exposed to the infectious agent, but has not

yet been diagnosed as affected; inhibiting the infection, ie., arresting its development; or relieving or ameliorating the effects of the infection, ie., cause regression of the effects of the infection.

According to a fifth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of general formula (I) and a pharmaceutically acceptable carrier.

The pharmaceutical compositions according to one embodiment of the invention are prepared by bringing a compound of general formula (I) into a form suitable for administration to a subject using carriers, excipients and additives or auxiliaries.

Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412,1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's The Pharmacological Basis for Therapeutics (7th ed.).

The pharmaceutical compositions are preferably prepared and administered in dosage units. Solid dosage units include tablets, capsules and suppositories. For treatment of a subject, depending on activity of the

compound, manner of administration, nature and severity of the disorder, age and body weight of the subject, different daily doses can be used. Under certain circumstances, however, higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals.

The pharmaceutical compositions according to the invention may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the microbial infection and the weight and general state of the subject. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in situ* administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of the cytotoxic side effects. Various considerations are described, eg., in Langer, Science, 249: 1527, (1990). Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients may be suspending agents such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a

condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as those mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents which may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of general formula (I) may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Dosage levels of the compound of general formula (I) of the present invention will usually be of the order of about 0.05mg to about 20mg per kilogram body weight, with a preferred dosage range between about 0.05mg to about 10mg per kilogram body weight per day (from about 0.1g to about 3g per patient per day). The amount of

active ingredient which may be combined with the carrier materials to produce a single dosage will vary, depending upon the host to be treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 1mg to 1g of an active compound with an appropriate and convenient amount of carrier material, which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5mg to 500mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In addition, some of the compounds of the invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The compounds of the invention may additionally be combined with other compounds to provide an operative combination. It is intended to include any chemically compatible combination of pharmaceutically-active agents, as long as the combination does not eliminate the activity of the compound of general formula (I) of this invention.

According to a sixth aspect of the present invention there is provided a method of killing a microorganism, comprising exposing said microorganism to a compound of general formula (I) as defined above.

Advantageously, although not limited to, the microorganism is selected from the group consisting of *Mycobacterium* including *Mycobacterium tuberculosis*, *M. avium intracellulare*, *M. fortuitum*, *M. abscessus* and rapid growing atypical Mycobacterial strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus* and *S.*

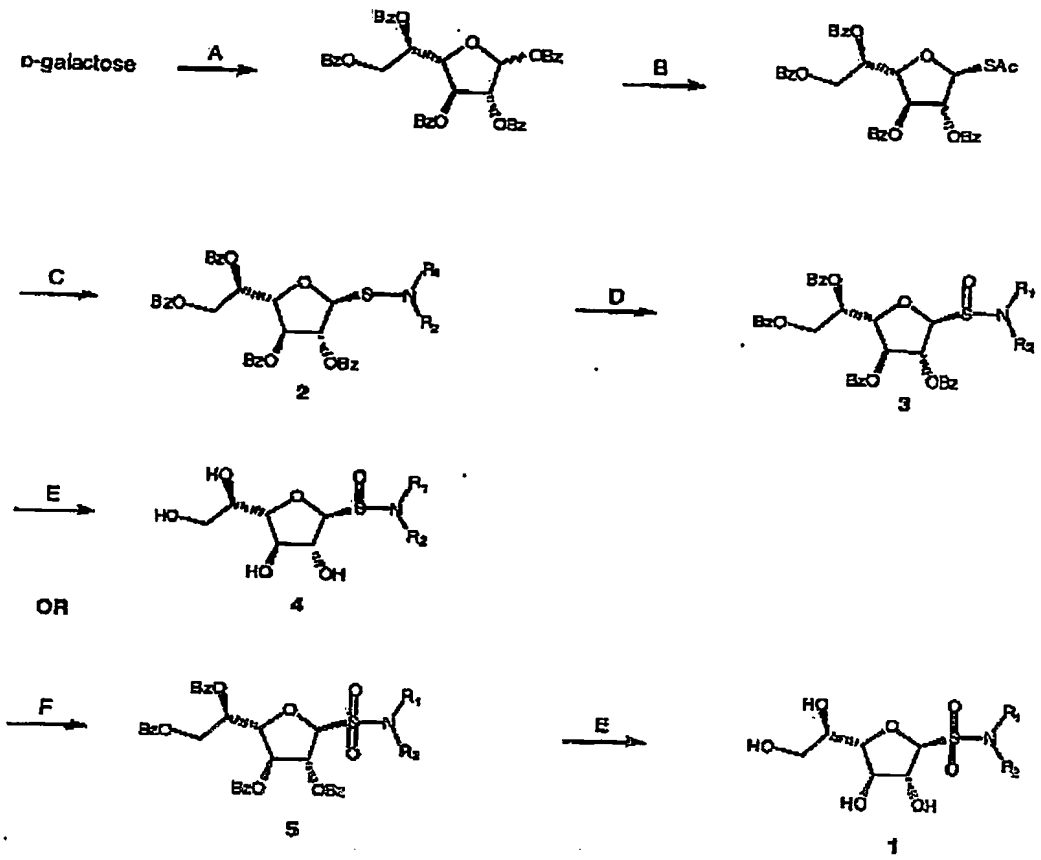
aureus (Coagulas-negative) and *Enterococci* species.

Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Modes for Performing the Invention

The synthetic scheme to be employed to prepare compounds in accordance with preferred embodiments of the invention is now described in more detail. For the preparation of Examples 1 to 4, per-*O*-benzoylated Galf sulfenamide (compound 2) is prepared according to known literature methods (Owen & von Itzstein, 2000) and is shown in Scheme 1 without modification. The synthesis of protected (compounds 3 and 5; Example 1 and 2) and deprotected (compounds 4 and 1; Examples 3 and 4) galactofuranosyl *N,N*-dialkylsulfinamides and *N,N*-dialkylsulfonamides is described in Scheme 1.

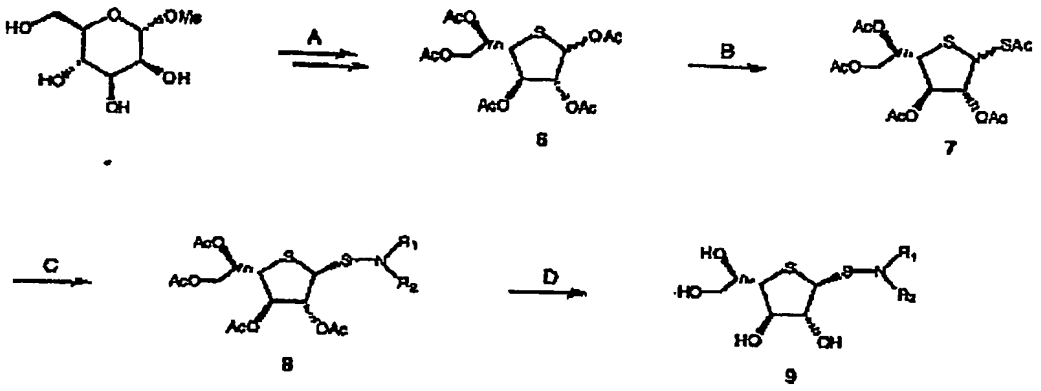


Scheme 1

Reagents and Conditions: A) i) Pyr, 100°C, 1 h, ii) BzCl, 60°C, 2 h, iii) rt, 24 h; B) $SnCl_4$, CH_2Cl_2, HSAc, rt, 1 h, N_2; C) $BrCH(COOEt)_2$, DMF, THF, HNR_1R_2, rt/40°C, 12-80 h, N_2; D) i) *N*-chlorosuccinimide, CH_2Cl_2, 0°C, 30 min., ii) $H_2O/KHCO_3$, According to Haake *et al.*, 1979; E) NaOMe, MeOH, rt, 2 h, N_2; F) mCPBA, reflux, 12 h, According to Glass & Swedo, 1977.

For the preparation of Examples 5, 6 and 7, per-O-acetylated 4-thio-Galf (compound 6) is prepared according to known literature methods (Varela, Cicero and de Lederkremer, 1989) and is shown in Scheme 2 without modification. The synthesis of protected (compound 8; Example 6) and deprotected (compound 9; Example 7) 4-thio galactofuranosyl *N,N*-dialkylsulfenamides is described in

Schema 2.



Scheme 2

Reagents and Conditions: A) According to Varela et al. 1989; B) $SnCl_4$, CH_2Cl_2, HSAc, rt, 1 h, N_2; C) $BrCH(COOEt)_2$, DMF, THF, HNR_1R_2, rt/40°C, 12-80 h, N_2; D) NaOMe, MeOH, rt, 2 h, N_2.

Example 1

N,N-Dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl) sulfinamide 3 (R_1 = R_2 = octyl).

A solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfenamide 2 in CH_2Cl_2, is added dropwise to a stirred and cooled solution of *N*-chlorosuccinimide in CH_2Cl_2. Stirring is continued for 15-30 minutes. After this time sat. aq. potassium hydrogen carbonate is added with stirring. The organic layer is separated and dried over potassium carbonate, and the solvent is then removed under reduced pressure. The residue is chromatographed to yield *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-1-thio-β-D-galactofuranosyl) sulfinamide.

Example 2

N,N-Dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl) sulfonamide 5 (R_1 = R_2 = octyl).

To a solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfinamide 3 in THF, is added m-chloroperoxybenzoic acid (85%, 3 equiv.). The reaction is stirred under reflux for 12 h. After this time the solvent is removed under reduced pressure. The residue is chromatographed to yield *N,N*-Dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranosyl)sulfonamide.

Example 3

N,N-Dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfinamide 4 (R_1 = R_2 = octyl).

To a solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1,4-thio-β-D-galactofuranosyl) sulfinamide 3 in dry MeOH is added one equivalent of NaOMe (1M solution in dry MeOH). The reaction is stirred at rt for 2 h under N_2. After this time the solution is neutralised with Amberlite IR 120 (H^+) resin, filtered, and the solvent removed under reduced pressure. The residue is chromatographed to yield *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl) sulfinamide.

Example 4

N,N-Dioctyl-*S*-(1-thio-β-D-galactofuranosyl)sulfonamide 1 (R_1 = R_2 = octyl).

To a solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-1,4-thio-β-D-galactofuranosyl) sulfonamide 5 in dry MeOH is added one equivalent of NaOMe (1M solution in dry MeOH). The reaction is stirred at rt for 2 h under N_2. After this time the solution is neutralised with Amberlite IR 120 (H^+) resin, filtered, and the solvent removed under reduced pressure. The residue is chromatographed to yield *N,N*-dioctyl-*S*-(1-thio-β-D-galactofuranosyl) sulfonamide.

Example 5

1-*S*-Acetyl-2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranose 7.

To a stirred solution of 1,2,3,5,6-penta-*O*-acetyl-4-thio-α/β-D-galactofuranose 6 [Varela *et al.* 1989] in dry CH_2Cl_2 at 0 °C, under N_2 is added tin tetrachloride (1.2 equiv.). After 10 minutes thiolacetic acid (2 equiv.) is added and the reaction is stirred for 2 h at 0 °C under N_2. After this time the reaction is diluted with sat. aq. $NaHCO_3$ (150 mL) and EtOAc (150 mL). The layers are separated and the organic layer is washed once with sat. aq. $NaHCO_3$ (150 mL) and once with aq. NaCl (150 mL). The organic phase is then dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue is chromatographed (hexane-EtOAc 2:1) to furnish 1-*S*-acetyl-2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranose.

Example 6

N,N-Dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranosyl) sulfenamide 8 (R_1 = R_2 = octyl).

1-*S*-Acetyl-2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranose 7 is dissolved in dry THF. Diethylbromomalonate (2 equiv.) is then added, and the mixture is stirred for 10 minutes at rt under argon. Dioctylamine (4 equiv.) is then added and the reaction is stirred for 60 h at rt under N_2. After this time the volatile compounds are removed under reduced pressure. The residue is then diluted in EtOAc (100 ml) and washed twice with sat. NaCl (2 x 100 ml), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue is chromatographed (hexane-EtOAc 4:1) to furnish *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranosyl) sulfenamide.

Example 7

N,N-Dioctyl-*S*-(4-thio-β-D-galactofuranosyl) sulfenamide 9 (R_1 = R_2 = octyl).

To a solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-4-thio-β-D-galactofuranosyl) sulfenamide 8 in dry MeOH is added one equivalent of NaOMe (1M solution in dry MeOH). The reaction is stirred at rt for 2 h under N_2. After this time the solution is neutralised with Amberlite IR 120 (H^+) resin, filtered, and the solvent removed under reduced pressure. The residue is chromatographed (EtOAc) to yield *N,N*-dioctyl-*S*-(4-thio-β-D-galactofuranosyl) sulfenamide.

Industrial Applicability

The compounds of general formula (I) are pharmaceutical agents, particularly anti-microbial agents.

References

The disclosure of the following documents is incorporated herein by reference:

von Itzstein, M.; Wu, W-Y.; Kok, G.B.; Pegg, M.S.; Dyason, J.C.; Jin, B.; Phan, T.V.; Smythe, M.L.; White, H.F.; Oliver, S.W.; Colman, P.M.; Varghese, J.N.; Ryan, D.M.; Woods, J.M.; Bathell, R.C.; Hotham, V.J.; Cameron, J.M.; Penn, C.R. *Nature* 1993, *363*, 418-423.

Kok, G.B.; Campbell, M.; Mackey, B.; von Itzstein, M. *J. Chem. Soc., Perkin Trans. 1* 1996, 2811-2815.

Fazli, A.; Bradley, S.J.; Kiefel, M.J.; Jolley, C.; Holmes, I.H.; von Itzstein, M. *J. Med. Chem.* 2001, *44*, 3292-3301.

Owen, D. J.; von Itzstein, M. *Carbohyr. Res.* 2000, *328*, 287-292.

Marino, C.; Marino, K.; Miletti, L. C.; Alves, M. J. M.; Colli, W.; de Lederkremer, R. M. *Glycobiology* 1998, *8*, 901-904.

Miletti, L. C.; Marino, C.; Marino, K.; de Lederkremer, R. M.; Colli, W.; Alves, M. J. M. *Carbohydr. Res.* 1999, *320*, 176-182.

Zhang, Q.; Liu, H. *J. Am. Chem. Soc.* 2001, *123*, 6756-6766.

Brimacombe, J.; Gent, P.; Stacey, M. *J. Chem. Soc. Org.* 1968, 567-569.

Brimacombe, J.; Da'aboul, I.; Tucker, L. *J. Chem. Soc. Org.* 1971, 3762.

Lemieux, R. U.; Stick, R. V. *Aust. J. Chem.* 1975, *28*, 1799-1801.

de Lederkremer R. M.; Cirelli, A.; Sznaidman, M. L. *Carbohydr. Res.* 1986, *146*, 233-240.

Shin, J.; Perlin, A. *Carbohydr. Res.* 1979, *76*, 165-176.

de Lederkremer R. M.; Cicero, D.; Varela, O. *Tetrahedron* 1990, *46*, 1131-1144.

de Lederkremer, R. M.; Marino, K.; Marino, C. *Anal. Biochem.* 2002, *301*, 325-328.

Pathak, A. K.; Pathak, V.; Suling, W. J.; Gurcha, S. S.; Morehouse, C. B.; Besra, G. S.; Maddry, J. A.; Reynolds, R. C. *Bioorg. Med. Chem.* 2002, *10*, 923-928.

Ernst, B.; Hart, G. W.; Sinay, P. (Eds), *Carbohydrates in Chemistry and Biology*, Wiley-VCH, Weinheim, 2000, Vols 1 – 4.

Chapleur, Y. *Carbohydrate Mimics*, Wiley-VCH, Weinheim, 1998.

Lillelund, V.H.; Jensen, H.H.; Liang, X.; Bols, M. *Chem. Rev.* 2002, *102*, 515-553.

Craine, L.; Raban, M. *Chem.Rev.* 1989, *89*, 589-712.

Glass, R.S.; Swedo, R.J. *Synthesis* 1977, 798-800.

Haake, M.; Gebbing, H.; Benack, H. *Synthesis* 1979, 97.

Varela, O.; Cicero, D.; de Lederkremer R. M. *J. Org. Chem.* 1989, *54*, 1884-1890.

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